Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials


CRD summary
This review assessed the effects of starting statin therapy within 14 days of the onset of acute coronary syndrome. The authors concluded that early statin therapy does not reduce death, myocardial infarction or stroke up to 4 months, but may reduce unstable angina. This was a well-conducted and clearly reported review and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To assess the effects of early statin therapy on relevant clinical outcomes (death, myocardial infarction (MI) and stroke) in patients with acute coronary syndrome (ACS).

Searching
MEDLINE, EMBASE and Pascal (all from inception to August 2005) and the Cochrane CENTRAL Register (Issue 2, 2005) were searched without language restrictions; the search terms were reported. Reference lists of identified studies, recently published editorials and reviews were also screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a follow-up of at least 30 days were eligible for inclusion.

Specific interventions included in the review
Studies that compared early statin therapy (within 14 days of the onset of ACS) with placebo or usual care were eligible for inclusion. Studies that compared two different statins were excluded. Studies of cerivastatin were only included in the sensitivity analysis as this statin has been withdrawn from the market. The included studies evaluated pravastatin, atorvastatin, fluvastatin and simvastatin. Usual care was defined as conventional medical treatment and optional lipid-lowering therapy.

Participants included in the review
Studies of patients with ACS (MI or unstable angina) were eligible for inclusion. Studies of patients who had previously received heart transplantation were excluded. The included studies were predominantly in men (range: 58 to 93% of the participants) and the mean age ranged from 53 to 69 years. The prevalence of cardiovascular risk factors varied among studies: diabetes ranged from 0 to 59%, hypertension from 18 to 90%, current smokers from 28 to 80%, and prior MI from 0 to 85%.

Outcomes assessed in the review
The primary end point was the combined outcome of nonfatal MI, nonfatal stroke and total death. Secondary individual outcomes were total death, total MI, total stroke, cardiovascular death, fatal MI, nonfatal MI, revascularisation procedures and unstable angina (recurrent myocardial ischaemia requiring emergency hospitalisation). The outcomes were assessed at 1 and 4 months. The review also assessed lipid-lowering effects and adverse events at the end of follow-up.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies. The methods used to resolve any disagreements were not reported.

Assessment of study quality
Studies were assessed for adequacy of allocation concealment, blinding of the patients, caregivers or assessors of clinical outcomes, and the proportion of patients with complete clinical follow-up.

Two reviewers independently assessed validity. The methods used to resolve any disagreements were not reported.

**Data extraction**

Two reviewers independently extracted the data. The methods used to resolve any disagreements were not reported. The authors of the included studies were contacted for additional data; the reviewers were unable to contact the authors of one trial. The number of patients with each outcome of interest was extracted at the 1- and 4-month follow-ups and used to calculate risk ratios (RRs) with 95% confidence interval (CIs). For one study data were only extracted for the subgroup of patients with unstable angina.

**Methods of synthesis**

**How were the studies combined?**

The studies were combined using a random-effects meta-analysis. Pooled RRs with 95% CIs were calculated separately for each outcome of interest. A funnel plot was used to assess publication bias. A post hoc analysis was undertaken to estimate the power of the meta-analysis to detect a treatment difference.

**How were differences between studies investigated?**

Statistical heterogeneity was assessed using the Cochran Q test. The inconsistency of treatment effects was also measured. Pre-specified sensitivity analyses were performed to examine the influence of quality components, time to starting statins (within 3 days versus up to 14 days) and type of statin. A post hoc sensitivity analysis was performed in which data from an unpublished trial of cerivastatin was included.

**Results of the review**

Twelve RCTs (n=13,024) were included.

Combined primary outcome (death, MI and stroke): there was no statistically significant difference between early statins and control for the combined outcome at 1 month (RR 0.93, 95% CI: 0.80, 1.09, P=0.39) based on 12,885 patients in 10 RCTs, or 4 months (RR 0.93, 95% CI: 0.81, 1.07, P=0.30) based on 9,469 patients in 10 RCTs. There was no evidence of statistical heterogeneity for either meta-analysis. The sensitivity analysis showed that the results were similar when only higher quality trials were included, for time of initiation of statin therapy, and for different types of statins.

Secondary outcomes: the reduction in unstable angina at 4 months just reached statistical significance for early statin treatment compared with control (RR 0.80, 95% CI: 0.64, 1.00, P=0.05). Moderate heterogeneity was found, which the authors attributed to differences in the definition of unstable angina across studies.

There was no statistically significant difference between early statin treatment and control at 1 or 4 months for total death, total MI, total stroke, cardiovascular death, fatal or nonfatal MI, revascularisation procedures or for unstable angina at 1 month follow-up (the results were reported).

Lipid-lowering effect: the mean reduction in low-density lipoprotein cholesterol ranged from -15% to -53%, while the mean reduction in cholesterol ranged from -9% to -37%.

Adverse effects: myopathy was found in 0.1% (n=9) of patients taking statins compared with 0.06% (n=4) of those taking placebo. All statin-related cases were taking high-dose (80 mg/day) simvastatin. Rhabdomyolysis was found in 3 patients taking statins. There were no fatalities. Increases in liver transferase levels to more than 3 times normal were found in 1.1% (n=75) of patients taking statins compared with 0.4% (n=28) of those taking placebo.

The authors estimated that the meta-analysis had 73% power of detecting a 16% treatment difference in the combined outcome.
Authors’ conclusions
Starting statin treatment within 14 days of the onset of ACS does not reduce death, MI or stroke up to 4 months, but it may reduce the risk of unstable angina.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched without language restrictions and attempts were made to locate unpublished data, thus minimising the possibility of language and publication bias. The potential for publication bias was tested and no evidence of its presence was found. Two reviewers independently selected studies for inclusion, assessed validity and extracted the data, thus reducing the potential for reviewer bias and errors. Validity was assessed using established criteria and the results of the assessment were reported.

Adequate details of each included study were presented and statistical heterogeneity was assessed. The decision to statistically combine the studies appeared appropriate, as was the meta-analysis technique used. The influence of various factors including quality criteria was examined. In addition, the authors calculated the power of the meta-analysis to detect a treatment difference. This was a well-conducted and clearly reported review and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the review findings supported recommendations to start statin therapy prior to hospital discharge in all patients with ACS. They stated that the results supported the safety of current guidelines (see Other Publications of Related Interest nos.1-2).

Research: The authors did not state any implications for further research.

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Other publications of related interest

This additional published commentary may also be of interest. Carey BC, Berger PB. Review: early statin therapy does not reduce the composite endpoint of death, MI, or stroke in acute coronary syndromes. ACP J Club 2006;145:61.
Indexing Status
Subject indexing assigned by NLM

MeSH
Angina, Unstable /drug therapy; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /therapeutic use; Morbidity; Mortality; Myocardial Infarction /epidemiology /prevention & control; Myocardial Ischemia /drug therapy; Randomized Controlled Trials as Topic; Stroke /epidemiology /prevention & control

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.